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(54) Title: INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS AND NERVE AXON MYELIN

(57) Abstract: A method of treatment of and composition for human degenerative neurologic diseases discloses the administration of therapeutically amounts of an enhancement agent, such as thrombopoietin, to enhance the repair of neurons, including re-myelination. A regulatory agent, such as thyroid hormone or thyrotropin, may also be included as part of the method and composition as a regulator of cell division and oligodendroglia production.



WO 01/13936 A1

**INDUCED REGENERATION AND REPAIR OF DAMAGED NEURONS
AND NERVE AXON MYELIN**

BACKGROUND OF THE INVENTION

5 This PCT application claims priority of U.S. Patent Application Serial No. 09/_____,
entitled "Method of Enhancement of Neurologic Recovery in Human Nervous System Damage
by Use of Pharmaceutical Thrombopoietin", to George R. Schwartz, filed on August 17, 2000,
which is a continuation-in-part application of U.S. Patent Application Serial No. 09/_____,
entitled "Method of Enhancement of Neurologic Recovery in Human Nervous System Damage
10 by Use of Pharmaceutical Thrombopoietin", to George R. Schwartz, filed on June 5, 2000, which
in turn is a continuation-in-part of U.S. Patent Application Serial No. 09/499,198, entitled "Method
of Enhancement of Neurologic Recovery in Human Nervous System Damage by Use of
Pharmaceutical Thrombopoietin," to George R. Schwartz, filed February 7, 2000, now
abandoned, and which claimed the benefit of U.S. Provisional Application Serial No. 60/150,040 ,
15 entitled "Method of Enhancement of Neurologic Recovery in Human Nervous System Damage
by Use of Pharmaceutical Thrombopoietin", to George R. Schwartz, filed August 20, 1999. The
specification of each of the foregoing is incorporated herein by reference.

Field of the Invention (Technical Field):

20 This invention relates to treatment of human neurologic damage, and in particular to a
method for increased regeneration and repair of damaged neurons and nerve axon myelin
coatings, and nerve cell repair.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

25 (BEST MODES FOR CARRYING OUT THE INVENTION)

Demyelination occurs when the myelin coating around nerve axons degenerates resulting
in a defect in the ability to transmit nerve impulses. For example, multiple sclerosis is a disease

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of unknown cause in which degeneration occurs in the myelin sheath surrounding the nerves.

This demyelination is also found in many other diseases such as transverse myelitis.

Demyelination also occurs after trauma to the brain or spinal cord, after a stroke, in

neurodegenerative diseases such as amyotrophic lateral sclerosis and Alzheimer's disease, as

5 well as in viral diseases including AIDS.

A cell type in the nervous system called the oligodendroglia is intimately involved in myelin regeneration, repair and maintenance of the nerve cells. Repair occurs by the repetitive wrapping of the plasma membranes of the oligodendroglia cells around damaged nerve cells and
10 offers continuing metabolic nerve cell support. In the art, it has been established that for O-2A progenitor cells that produce oligodendroglia cells proliferation is induced in culture by type-1 astrocytes. A recognized mitogen for O-2A progenitor cells is platelet-derived growth factor (PDGF), and PDGF is a potent mitogen for O-2A progenitor cells in vitro. Thus, laboratory experimentation has suggested that PDGF is crucial for the control of nerve cell repair and
15 myelination in the nervous system.

It is also known in the art that the development of oligodendrocytes from precursor cells also includes an effector component which depends on thyroid hormone that stops cell division and initiates differentiation at the appropriate time.

20

Further, it is also known in the art that proteins generally referred to as thrombopoietins support biological activity that ultimately results in the production of platelets and other cells from the myeloid line, including markedly increasing PDGF production. Methods of preparation of thrombopoietin are disclosed in recent patents, for example, U.S. 5,795,569 issued to Amgen, Inc. and processes for producing them by recombinant genetic engineering techniques are also
25 disclosed. Hence, the availability of thrombopoietins in pharmaceutically available quantities is to be expected in the near future.

SUMMARY OF THE INVENTION

A method of treatment of degenerative neurologic diseases provides for the administration of therapeutically effective amounts of an enhancement agent, such as
5 thrombopoietin, to enhance the regeneration of neuron cells. A regulatory agent, such as thyroid hormone or thyrotropin, may also be included as a regulator of cell division and differentiation. The method may be used with humans and also with other mammals with neurologic damage.

The thrombopoietin may be orally ingested by the patient, or may be administered by
10 intravenous, intramuscular or intrathecal injection.

The method can further include the step of administering thyroid hormone to the patient. The thyroid hormone may be orally ingested by the patient, or may be administered by intravenous, intramuscular or intrathecal injection. The thyroid hormone may include thyroid
15 hormone extract or synthetic thyroid hormone.

The method can also further include the step of stimulating human thyroid production by administering thyrotropin to the patient. The thyrotropin may be orally ingested by the patient, or may be administered by intravenous, intramuscular or intrathecal injection.

20

The thrombopoietin may be isolated from a mammal, made by recombinant means, or made by synthetic means. It may be human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin. The therapeutically effective amount of thrombopoietin ranges from about 1.0 to about 100 µg/kg body weight per day.

25

In the method of this invention, the thyroid hormone can be co-administered to the patient with the thrombopoietin. In an alternative method, the thyrotropin can be co-administered to the patient with the thrombopoietin.

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The invention further consists of a pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyroid hormone. The composition can contain between about 0.07 to about 10 mg of thrombopoietin per dose unit. The composition may be formulated such that it contains between about one and about three
5 times as much thyroid hormone as thrombopoietin. In this composition, the thrombopoietin may be isolated from a mammal, made by recombinant means, or made by synthetic means. The thrombopoietin may be human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin. The thyroid hormone may be thyroid hormone extract or synthetic thyroid hormone.

10

The invention further consists of a pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyrotropin. The composition can contain between about 0.07 to about 800 mg of thrombopoietin per dose unit. In this composition, the thrombopoietin may be isolated from a mammal, made by recombinant means,
15 or made by synthetic means. The thrombopoietin may be human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin.

A primary object of the present invention is to provide a method and formulation for neuron or myelin regeneration and maintenance in the nervous system.

20

Another object of the present invention is to provide a method for neuron and myelin regeneration and maintenance using endogenous platelet-derived growth factor (PDGF), production of which is induced by use of an enhancement agent.

25

Another object of the present invention is to increase PDGF production by administration of a therapeutically effective amount of thrombopoietin (TPO).

Another object of the invention is to provide a regulatory agent which effects a decrease in the rate of cellular division of oligodendrocytes and initiates differentiation into functional

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neuronal support cells.

Another object of the invention is to provide a method for treatment of neurological disorders including administration of TPO and co-administration or sequential administration of a regulatory agent, such as thyroid hormone, thyrotropin or the like.

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Other objects, advantages and novel features, and further scope of applicability of the present invention will be set forth in part in the detailed description to follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and
10 attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

(BEST MODES FOR CARRYING OUT THE INVENTION)

15

The present invention discloses a method of treatment of peripheral and central neurological diseases by the administration to patients of an enhancement agent in appropriate form and quantity. The treatment is disclosed for nervous system disorders, including diseases such as transverse myelitis, multiple sclerosis, demyelination occurring after trauma to the brain
20 or spinal cord, as well as stroke, degenerative diseases such as Alzheimer's and amyotrophic lateral sclerosis, and viral diseases such as AIDS, as well as peripheral nerve injury. The enhancement agent serves to stimulate the production of oligodendroglia and other glial cells in the repair of damaged neurons and nerve axons incident to such diseases.

25

The enhancement agent may be thrombopoietin which may be administered as a liquid or solid in the form of oral tablets, intravenous injection, intrathecal injection or intramuscular injection, depending upon the course of therapy followed.

30

In a second embodiment of the invention, a regulatory agent is used, which may be thyroid hormone in the form of thyroid extract, stimulation of human production by thyrotropin

(thyroid-stimulating hormone), or synthetic thyroid hormone combined with the enhancement agent therapy to regulate cell division and oligodendroglia production.

Prior to describing the present invention in detail, the following definitions are given:

5

Enhancement agent: Includes any substance which, when administered to a mammal, results in the direct or indirect production of platelet-derived growth factor (PDGF). Examples of enhancement agents include thrombopoietin (TPO) and other mpl ligands, variants and derivatives thereof, and the like.

10

Thrombopoietin: Includes TPO produced by any means, including TPO isolated from a mammal, made by recombinant means and made by synthetic means. TPO may be human TPO, a fragment of human TPO, a variant polypeptide of TPO, a chimeric polypeptide of any of the foregoing and the like. The TPO may further be modified, and may be pegylated, glycosolated and the like. The TPO may further be present in a formulation including one or more carriers or excipients. Various forms and formulations of TPO are described in, among others, U.S. Patent Nos. 5,795,569; 5,879,673; and 5,989,537.

15

Regulatory agent: Includes any substance which, when administered to a mammal, results in the direct or indirect alteration of cell division rates and induction of differentiation, specifically of oligodendrocyte cells. Regulatory agents include thyroid hormone, thyrotropin and the like. The effort of these regulatory agents are described generally in Rodriguez-Pena A: Oligodendrocyte development and thyroid hormone. *J. Neurobiol* 1999, Sep. 15;40(4):497-512; Ahlgren SC, Wallace H, Bishop J, Neophytou C, Raff MC: Effects of thyroid hormone on embryonic oligodendrocyte precursor cell development in vivo and in vitro. *Mol Cell Neurosci* 1997;9(5/6):420-32; Gao FB, Apperly J, Raff M: Cell-intrinsic timers and thyroid hormone regulate the probability of cell-cycle withdrawal and differentiation of oligodendrocyte precursor cells. *Dev Biol* 1998 May 1;197(1):54-66; Ahlgren SC, Wallace H, Bishop J, Neophytou C, Raff MC: Effects of thyroid hormone on embryonic oligodendrocyte precursor cell development in vivo and in vitro. *Mol Cell Neurosci* 1997;9(5/6):420-32; and Durand B, Raff M: A cell-intrinsic

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timer that operates during oligodendrocyte development. Bioessays 2000 Jan; 22(1):64-71. The thyroid hormone, thyrotropin or the like may be isolated from a mammal, made by synthetic means, made by recombinant means, or made by any means known in the art. The regulatory agent may further be present in a formulation including one or more carriers or excipients.

5

The methods and substances of this invention may be used in the treatment of any of a variety of conditions resulting in neurological damage, including peripheral and central nervous system (CNS) injury, disease or disorders. CNS disorders encompass numerous afflictions such as neurodegenerative diseases (e.g. Alzheimer's and Parkinson's), acute brain injury (e.g. stroke, head injury, cerebral palsy) and a large number of CNS dysfunctions (e.g. depression, epilepsy, schizophrenia). In recent years neurodegenerative disease has become an important concern due to the expanding elderly population which is at greatest risk for these disorders. These diseases include Alzheimer's disease, multiple sclerosis (MS), Huntington's disease, amyotrophic lateral sclerosis, and Parkinson's disease. CNS disorders also encompass CNS trauma, such as results from stroke, epilepsy, traumatic injury and the like. Further, many viral diseases, including AIDS, result in CNS disorders.

The enhancement agent may be formulated as set forth above, and administered by any art conventional means. In the case of TPO, a therapeutically effective amount is administered, resulting in PDGF expression. Relatively low dosages may be employed, from about 1.0 to about 100 µg/kg body weight of the patient, and preferably about 5 to about 10 µg/kg body weight.

The TPO can be administered through various routes including via the nose or lung, cutaneously, subcutaneously, intrathecally, and preferably intravenously. Depending upon the route of administration, the TPO is preferably administered in combination with an appropriate pharmaceutically acceptable carrier or excipient. When administered systemically, the therapeutic composition should be pyrogen-free and in a parenterally acceptable solution. These conditions are generally well known and accepted to those of skill in the appropriate art.

30

Briefly, dosage formulations of the materials of the present invention are prepared for storage or administration by mixing the compound having the desired degree of purity with physiologically acceptable carriers, excipients and/or stabilizers. Such materials may include buffers such as phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight peptides such as polyarginine, proteins such as serum albumen, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid or arginine; monosaccharides, disaccharides and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans; chelating agents such as EDTA; sugar alcohol such as mannitol or sorbitol; counter-ions such as sodium and/or non-ionic surfactants such as Tween, Pluronic or polyethyleneglycol. The TPO may be administered as the free acid or base form or as a pharmaceutically acceptable salt.

The TPO may be administered in sustained-release formulations, including polymeric substrates, hydrogels, liposomes and the like.

The regulatory agent may similarly be formulated as set forth above, and administered by any art conventional means. In the case of thyroid hormone, therapeutically effective amounts may be employed, resulting in a decrease in cellular division of oligodendrocytes and further differentiation into functional neuronal repair cells.

Any of a variety of thyroid hormones may be employed as a regulatory agent, including but not limited to purified thyroid, levothyroxine, liothyronine, and thyroglobulin. These are available in oral tablet formulations, and in the case of levothyroxine, additionally as an injectable parenteral. In usual oral dosage forms, from about 0.10 to 0.125 mg per day of levothyroxine is administered, for liothyronine sodium from about 25 to 50 µg per day is administered, for thyroglobulin from about 32 to 160 µg per day is administered, and for dessicated thyroid from about 15 to 120 mg per day is administered. Combinations of the foregoing may also be administered, such as liotrix, a combination of levothyroxine and liothyronine. Injectable levothyroxine, from about 50 to 200 µg per day, may be injected into a muscle or into a vein.

Thyrotropin, also called thyroid-stimulating hormone, may alternatively be employed to increase endogenous thyroid production. Thyrotropin is available as an injectable parenteral. Thyrotropin may be produced by any means known in the art, including as a recombinant form of human thyroid-stimulating hormone. Sufficient thyrotropin is administered to increase thyroid
5 levels to that desired, with monitoring as required by any of a variety of available thyroid assays.

In one embodiment, a patient with a CNS disorder is administered from about 1 to 50 µg/kg body weight of TPO by intravenous injection, with such injections occurring every 2 days for a period of at least 8 days. At a suitable time, such as 10 days after the initial injection of
10 TPO, administration of thyroid hormone is initiated. The thyroid hormone administration, for example a Synthroid® preparation (levothyroxine), is at a rate of about 2 to 4 µg/kg body weight per day, and is continued for a suitable period, such as 21 days.

Multiple courses of therapy may be undertaken, such that TPO and thyroid hormone
15 administration are alternated. There may also be periods of time between courses of therapy in which periods may be fixed or may be related to the onset of symptoms of CNS disorder.

The enhancement agent and regulatory agent may be co-administered, as part of a single formulation. Thus, a treatment regimen may be employed in which both TPO and thyroid
20 hormone are co-administered. Alternatively, TPO may be initially administered without thyroid hormone and after a suitable period administration of a formulation including TPO and thyroid hormone or thyrotropin is initiated.

The invention is further illustrated by the following non-limiting examples.
25

Example 1

B6SJL-TgN(SOD1-G93A)1Gur strain mice were obtained from The Jackson Laboratory, Bar Harbor, ME. The transgene in these mice carries a high copy number of a mutant allele human SOD1 containing the Gly93 -->Ala (G93A) substitution (often referred to as G1H). Mice
30 progressively become paralyzed in one or more limbs, with paralysis due to loss of motor

neurons from the spinal cord. The mice are generally described in Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, Chen W, Zhai P, Sufit RL, Siddique T: Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. *Science* 264:1772-1775 (1994), and use of these mice as a
5 model of familial amyotrophic lateral sclerosis is described in Chiu AY, Zhai P, Dal Canto MC, Peters TM, Kwon YW, Prattis SM, Gurney ME: Age-dependent penetrance of disease in a transgenic mouse model of familial amyotrophic lateral sclerosis. *Mol Cell Neurosci* 6:349-362 (1995).

10 At 105 days following birth, mouse A began manifesting objective symptoms of limb paralysis. A protocol as described in **Table 1** was followed.

Table 1	
Days Following Birth	Administration
107	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
110	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
113	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
117	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin and 0.25 cc i.p. of a solution containing 500 µg/cc of thyrotropin releasing hormone
119	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
121	Synthroid®, 0.1 mg in 2 ounces of drinking water, ad libitum

The thrombopoietin was obtained from Rand D. Systems, Inc. (Minneapolis, MN) as carrier-free
15 recombinant thrombopoietin and the thyrotropin was obtained from Ferring Pharmaceuticals; both were administered by intraperitoneal (i.p.) injection. Synthroid®, a form of levothyroxine, was obtained from Flint Pharmaceuticals in 100 µg tablets.

At day 111, marked improvement was observed, with elimination of shaking and limpness
20 and improved muscle tone. At day 113, shaking resumed with observed early weakness developing. By day 115 marked hind limb weakness was observed. By day 118, decreased weakness was observed, although paresis remained in the left hind quarters. On day 120, increased mobility was observed. On day 122, marked improvement in front limbs was

observed. Recurrence and increasing front limb weakness was observed on day 124. The mouse died at day 126.

Example 2

5 A litter mate of mouse A, referred to as mouse B, was administered a protocol as described in **Table 2**, with administration commencing prior to the onset of any objective symptoms.

Table 2	
Days Following Birth	Administration
87	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
91	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
93	0.6 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
95	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
105	Synthroid®, 0.1 mg in 4 ounces of drinking water, ad libitum through remaining life
126	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin

10 With this protocol, no objective signs were observed until day 121, when slight posterior weakness was noted. This was 16 days following onset of objective signs of illness in the litter mate mouse A. At day 129, posterior limb paralysis was observed, with the fore limbs remaining functional but some weakness observed in the left front. The mouse died on day 132.

15 Example 3

 A B6SJL-TgN(SOD1-G93A)1Gur strain mouse as described in Example 1 was obtained, referred to as mouse C. Mouse C was administered a protocol as described in **Table 3**, with administration commencing prior to the onset of any objective symptoms.

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Table 3	
Days Following Birth	Administration
80	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
84	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
86	0.6 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
88	0.5 cc i.p. of a solution containing 1 µg/cc of thrombopoietin
92	Synthroid®, 0.1 mg in 4 ounces of drinking water, ad libitum through remaining life

With this protocol, no objective signs of illness were observed through day 110, more than two standard deviations from the expected onset of sickness (91 ± 14 days).

5 The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

10 Although the invention has been described in detail with particular reference to these preferred embodiments, other embodiments can achieve the same results. Variations and modifications of the present invention will be obvious to those skilled in the art and it is intended to cover in the appended claims all such modifications and equivalents. The entire disclosures of all references, applications, patents, and publications cited above are hereby incorporated by reference.

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CLAIMS

What is claimed is:

- 5 1. A pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyroid hormone.
2. A pharmaceutical composition for treatment of neurologic damage in a mammal, comprising thrombopoietin and thyrotropin.
- 10 3. The compositions of claim 1 or 2, comprising between about 0.07 to about 10 mg of thrombopoietin per dose unit.
4. The compositions of claim 1 or 2 wherein the thrombopoietin is a thrombopoietin isolated from a mammal, a thrombopoietin made by recombinant means, or a thrombopoietin made by synthetic means.
- 15 5. The compositions of claim 1 or 2 wherein the thrombopoietin is human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin.
- 20 6. The composition of claim 1 wherein the composition contains between about one and about three times the usual dose for thyroid hormone as for thrombopoietin.
- 25 7. A method of treatment of neurologic damage in a mammal, comprising the step of administering therapeutically effective amounts of thrombopoietin to the mammal.
8. The method of claim 7 further comprising the step of administering thyroid hormone to the mammal.

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9. The method of claim 7 further including the step of stimulating human thyroid production by administering thyrotropin.

10. The method of claim 7 wherein the step of administering the thrombopoietin
5 comprises orally ingesting the thrombopoietin, intravenously injecting the thrombopoietin, intramuscularly injecting the thrombopoietin, or intrathecally injecting the thrombopoietin.

11. The method of claim 8 wherein said step of administering the thyroid hormone
10 comprises orally ingesting the thyroid hormone, intravenously injecting the thyroid hormone, intramuscularly injecting the thyroid hormone, or intrathecally injecting the thyroid hormone.

12. The method of claim 8 wherein the step of administering the thyroid hormone comprises administering thyroid hormone extract or synthetic thyroid hormone.

15 13. The method of claim 9 wherein the step of administering the thyrotropin comprises orally ingesting the thyrotropin, intravenously injecting the thyrotropin, intramuscularly injecting the thyrotropin, or intrathecally injecting the thyrotropin.

14. The method of claim 7 wherein the thrombopoietin is a thrombopoietin isolated
20 from a mammal, a thrombopoietin made by recombinant means, or a thrombopoietin made by synthetic means.

15 15. The method of claim 7 wherein the thrombopoietin is human thrombopoietin, a fragment of human thrombopoietin, or a variant polypeptide of human thrombopoietin.

16. The method of claim 7 wherein the therapeutically effective amount ranges from about 1.0 to about 100 µg/kg body weight per day.

17. The method of claim 8 wherein the thyroid hormone is co-administered to the
30 mammal with the thrombopoietin.

18. The method of claim 9 wherein the thyrotropin is co-administered to the mammal with the thrombopoietin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/40683

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/00, 38/16

US CL : 514/2, 8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, HCAPLUS, WPIDS, MEDLINE, BIOSIS, EMBASE, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,E	Database Medline, US National Library of Medicine, (Bethesda, MD, USA), HEUER, H. et al. 'Expression of thyrotropin-releasing hormone receptor 2 (TRH-R2) in the central nervous system of rats,' abstract, J. Comp. Neurol. 11 December 2000, 428 (2), 319-36.	1-18
Y	Database Medline, US National Library of Medicine, (Bethesda, MD, USA), D'ALECY, L. 'Thyroid hormone in neural rescue,' abstract, Thyroid, 07 February 1997, 7 (1), 115-24.	1-18
A	Database Medline on STN (Columbus, OH, USA), No. 1999304855, NAKANISHI, K. et al. 'Thrombopoietin expression in normal and hypobaric hypoxia-induced thrombocytopenic rats,' abstract, Laboratory Investigation, June 1999, 79 (6), 679-88.	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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